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Short Communication

Long-term course of lung clearance index between infancy and school-age in cystic fibrosis subjects

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Abstract

Multiple breath washout (MBW) measurements have recently been shown to be sensitive for detection of early cystic fibrosis (CF) lung disease, with the lung clearance index (LCI) being the most common measure for ventilation inhomogeneity. The aim of this observational study was to describe the longitudinal course of LCI from time of clinical diagnosis during infancy to school-age in eleven children with CF.

Elevated LCI during infancy was present in seven subjects, especially in those with later clinical diagnosis. Tracking of LCI at follow-up was evident only in the four most severe cases.

We provide the first longitudinal data describing the long-term course of LCI in a small group of infants with CF. Our findings support the clinical usefulness of MBW measurements to detect and monitor early lung disease in children with CF already present shortly after clinical diagnosis.

Keywords: Lung function; Multiple-breath washout; Cystic fibrosis; Children; Longitudinal

1. Introduction

In children with cystic fibrosis (CF) small airway disease occurs early in life [1]. Recent cohort studies assessing bronchoalveolar lavage and computed tomography (CT) scans in infants with CF provided clear evidence of infection, inflammation, and altered structure of airways shortly after birth [2].

In older children, inert tracer gas multiple breath washout (MBW) has gained wide acceptance as a useful and sensitive marker to detect early characteristics of even mild CF lung disease [3]. Compared to spirometry and plethysmography, the lung clearance index (LCI) – the most commonly reported outcome from MBW as a measure of ventilation inhomogeneity – was the most sensitive functional outcome of structural airway abnormalities detected in CT scans [4–6]. Furthermore, it proved even to be a suitable primary outcome of randomized controlled trials assessing mucociliary clearance regimes in patients with mild CF lung disease [7,8].

The LCI has been shown to be already elevated in toddlers and school-age children with CF [6,9,10]. Moreover, recent longitudinal data suggest that abnormal LCI can be detected already in pre-school children and tracks into school-age despite normal spirometry and appropriate treatment [11]. Therefore, two imminent questions arise: whether the LCI is already abnormal in infants at the time of clinical CF diagnosis, and whether abnormal LCI in infancy tracks into school-age. While data on LCI in sedated infants with CF have been published [10,12], LCI data in unsedated infants with CF and the long-term course of infant LCI were not reported yet. We thus aimed

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to provide data on feasibility of MBW in unsedated infants and toddlers with CF, and complement current knowledge on early CF lung disease with the first longitudinal data on LCI from infancy to school-age.

2. Material and methods

A retrospective study design was applied to compare the LCI of eleven infants measured at time of clinical CF diagnosis with their follow-up LCI at early school-age (for demographics and clinical details see Table 1). This study was approved by the University Children's Hospital Ethics Committee, Bern, Switzerland. During clinical routine work-up MBW using an ultrasonic flowmeter is performed in infants at time of CF diagnosis since 1999 and at school-age since 2009. Both measurements in infants and school-aged children were done using the same standardized protocols throughout the entire study period.

Infant lung function was performed since then in 33 infants with CF. In infants, LCI was derived from MBW using 4% sulfur hexafluoride (SF_6) as tracer gas and a main-stream ultrasonic flowmeter setup (Exhalyzer D®; Eco Medics AG, Duernten, Switzerland) [13]. Infants were naturally sleeping, positioned supine with the head in midline, and were breathing through an infant facemask according to current standards [13–15]. Ten infants were excluded due to either need of sedation for MBW (n=5) or poor technical quality (n=5). From the remaining 23 children, 11 reached school-age during the study period and performed follow-up MBW. None of the infants or children showed evidence of an acute respiratory tract infection and/or signs of an exacerbation prior to (≤3 weeks) or at the day of both lung function measurements.

Follow-up LCI was derived from nitrogen MBW using 100% oxygen and a side-stream ultrasonic flowmeter setup (Exhalyzer D®; Eco Medics AG, Duernten, Switzerland) [16]. Follow-up MBW was performed in awake children in a sitting position breathing through a mouthpiece and wearing a nose clip.

In order to account for these methodological differences, we used previously reported [13,16] equipment- and tracer-gas-specific normative LCI data from 201 healthy infants and 39 healthy school-children, respectively, to calculate z-scores. Descriptive statistics were performed using Stata™ (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, USA).

3. Results

MBW in infants with CF was performed at median age (interquartile range, IQR) of 21.9 (14–45) weeks and at 9.7 (6.9–10.3) years at follow-up. Median (IQR, range) LCI at time of clinical CF diagnosis was 8.8 (7.2–10.5; 6.4–12) and at follow-up 7.2 (6.1–8.9; 5.9–10.4). LCI values of controls were 6.6 (6.3–7.1; 5.5–8.6) in 201 healthy infants and 5.5 (4.6–6.4, 4.2–6.8) in 39 healthy school-children, respectively. Elevated LCI was defined as LCI higher than two z-scores and was present in seven out of eleven infants with CF at time of clinical diagnosis (Figs. 1 and 2). Higher values were observed in infants who were older at time of diagnosis (Fig. 3). Tracking of LCI to follow-up was evident in the four most severe cases, while a more heterogeneous long-time course of LCI was observed in the seven other children. Three out of those showed an improvement of the LCI, whereas the LCI deteriorated in the other four children. One child (B) showed a severe deterioration of the LCI (Fig. 1) reflecting the clinical course of this child (Table 1).

4. Discussion

This is the first study assessing the long-term course of LCI in a small group of infants with CF. Preliminary data of normal LCI in infants diagnosed by CF new born screening (NBS) have

Table 1
Demographic and clinical details of children with CF.

Patient ID [a]	Gender [b]	Diagnosis	Genotype	Age at infant lung function (weeks)	Age at follow-up (years)	FEV1 at follow-up (z-score) [c]	Pseudomonas aeruginosa colonization [d]	Number of i.v. antibiotic treatments [e]	LCI tracking [f]
A	f	Failure to thrive	ΔF508del/ΔF508del	16.7	5.5	0.49	Twice	2	Deterioration
B	f	Meconium ileus	ΔF508del/unknown	5.1	6.9	−0.85	Intermittent	3	Severe deterioration
C	f	Failure to thrive	ΔF508del/ΔI507	21.9	10.1	−3.04	Intermittent	2	Improvement
D	f	Meconium ileus	ΔF508del/ΔF508del	16.9	10.8	−1.09	Twice	0	Deterioration
E	f	Meconium ileus	ΔF508del/ΔF508del	29.6	10.1	−1.48	Once	1	Consistently abnormal
F	f	Failure to thrive	ΔF508del/ΔF508del	14.0	8.2	−0.21	Never	0	Improvement
G	m	Failure to thrive	ΔF508del/R553X	82.6	10.3	−4.16	Intermittent	4	Consistently abnormal
H	m	Meconium ileus	ΔF508del/ΔF508del	2.0	6.0	−0.07	Intermittent	2	Deterioration
I	m	Failure to thrive	ΔF508del/ΔF508del	100.6	9.3	0.92	Once	0	Improvement
J	m	Meconium ileus	Q525X/Q525X	31.6	9.7	−1.04	Intermittent	2	Consistently abnormal
K	m	Failure to thrive	2347xdelG/N1303K	45.0	12.3	−2.26	Intermittent	5	Consistently abnormal

[a] Patient ID = identification (A to K; corresponding to figure symbols).
[b] Gender m = male, f = female.
[c] FEV1 z-scores were derived from published reference data [25].
[d] Number of positive *Pseudomonas aeruginosa* swabs between infancy and school-age MBW.
[e] Number of i.v. antibiotic treatments between infancy and school-age MBW.
[f] LCI course from infancy to school-age.

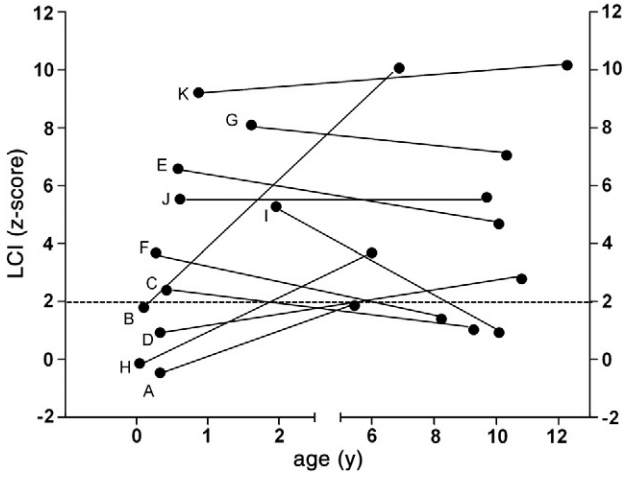

Fig. 1. Lung clearance index (LCI) as z-scores of eleven children at time of clinical CF diagnosis and at follow-up during school-age. Data are given as equipment-specific z-scores based on age-matched healthy controls. The *dashed line* represents the upper limit of normality.

challenged the usefulness of MBW in infants with CF [12]. Our results indicate that elevated LCI as marker of early CF lung disease can be detected already during infancy with non-invasive MBW measurements during natural sleep without sedation — which is important for practicability, more wide spread use and availability of reference values from healthy controls. LCI in our population was normal in infants with early diagnosis. LCI tended to increase in those with later clinical diagnosis, even though infants in our study had no respiratory symptoms immediately prior to or during MBW test occasions. This is in line with lung function data obtained in sedated infants with CF using both raised volume rapid thoracic compression (RVRTC) technique [17,18] and MBW [10,19]. All those findings suggest that structural changes in small airways start shortly after birth, accumulate over time and

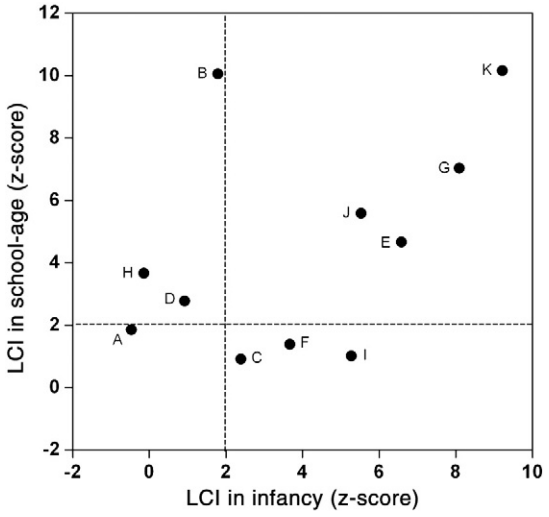

Fig. 2. Cross-plot of lung clearance index (LCI) z-scores obtained at infancy (*horizontal axis*) and school-age (*vertical axis*) in children with CF. The *dashed lines* represent the upper limits of normality.

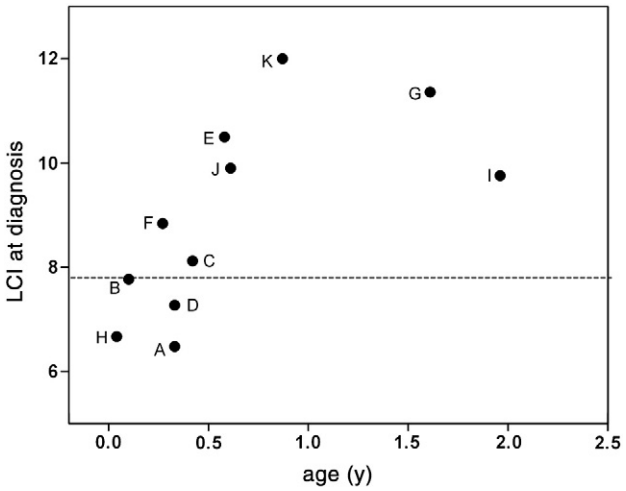

Fig. 3. Lung clearance index (LCI) of eleven infants at the time of clinical diagnosis. The *dashed line* represents the upper limit of normality.

subsequently reach a certain functional threshold quantifiable using MBW.

Given the retrospective study design and the small number of children, our data can only generate a hypothesis and should be confirmed in larger and prospective cohort studies. However these preliminary results suggest that there might be tracking of LCI from infancy to school-age. Recently Aurora et al. studied 48 children with CF from preschool to school-age [11]. Their results indicated tracking in 25 children and fluctuation of LCI in 23 children with predominantly abnormal LCI already at preschool-age. In our study LCI tracking was present in four out of eleven children and also seemed to be more pronounced in those infants with abnormal LCI at the time of clinical CF diagnosis. The inhomogeneous age distribution due to variable timing of CF diagnosis in our study may constrain generalizability for infants with CF diagnosed earlier by NBS. On the other hand, the age distribution in our study represents the wide range of time of clinical diagnosis and the natural course of CF lung disease during infancy.

We used different tracer gasses for MBW at baseline and follow-up visits. SF_6 is considerably less suitable for MBW in older children due to the need for higher SF_6 amounts during MBW measurements and thus higher workplace exposure and increased greenhouse gas effects. Nitrogen MBW requires washout procedures only and is more economic compared to SF_6, however pure oxygen is not suited for MBW in infants due to the induction of atelectasis and possible changes in breathing pattern [20,21]. In addition to those differences in tracer gasses [22], the differences in position (sitting or supine) [23], sleep or awake state [23], and different ratios of tidal volume over system dead space [24] make comparison of absolute LCI values between infancy and school-age in our study impossible. Consequently we used equipment- and method-specific z-scores derived from age-matched healthy controls to account for this.

In most of the countries in which regular infant lung function measurements have been performed, NBS for CF was introduced recently [2,19]. Thus we believe that these

longitudinal LCI data are unique, as studying the natural course of LCI in infancy after clinical diagnosis of CF only will not be possible in the future anymore.

In conclusion, MBW during natural sleep is feasible in infants with CF. The non-invasive method and the possibility to perform measurements without sedation make MBW an attractive lung function test possibly identifying those infants with the strongest need for intensified investigations and more aggressive treatment. Taken together, our findings support the ability of MBW to detect and monitor early CF lung disease in children.

5. Author's contribution

EK and FS contributed equally. Conception and design of the study: EK, FS, UF, NR, CC, PL. Acquisition of the data: EK, FS, OF, CA, PL. Analysis and interpretation of the data: EK, FS, OF, CC, PL. Drafting and revising: EK, FS, OF, CA, UF, NR, CC, PL. Important intellectual content: EK, FS, OF, UF, NR, CC, PL. Final approval: all authors.

6. Conflict of interest

The authors have no conflict of interest to report.

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